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Review

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A review of pain outcomes following targeted muscle reinnervation in lower extremity limb pain

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Abstract

Approximately 75% experience phantom (PLP), residual (RLP), or general (GLP) limb pain following lower extremity amputation. Targeted muscle reinnervation (TMR) is a peripheral nerve transfer that reroutes amputated nerves to motor endplates that can prevent or treat limb pain. This systematic review summarizes pain outcomes following primary and secondary treatment of lower extremity PLP, RLP, and GLP. Primary literature review of three databases - PubMed, EMBASE, MEDLINE - were used for all articles related to TMR and lower extremity limb pain, querying the same keywords: “targeted muscle reinnervation” AND “pain”. Citations were then reviewed and eliminated if only upper extremities were studied or the study lacked pain outcomes. Citations were categorized as primary or secondary TMR. Pain outcomes, including Numerical Rating Scales (NRS) and Patient-Reported Outcome Measurement Information System (PROMIS) Pain scores, were aggregated when appropriate. Ten studies met all inclusion and exclusion criteria after formal review for a total of 431 extremities, of which 79.1% (n = 341 limbs) were lower extremities. Average primary TMR PROMIS scores for PLP and RLP were lower than amputees without primary TMR. Average NRS scores and PROMIS Pain scores in secondary TMR demonstrated improvements in PLP, RLP, and GLP. Primary and Secondary TMR does prevent and improve PLP, RLP, and GLP; however, a minority of studies report quantifiable pain outcomes. All future TMR studies should include validated pain outcomes to better quantify the expected pain and quality of life improvements after lower extremity TMR.

Keywords: Lower extremity, amputation, phantom limb pain, residual limb pain, targeted muscle reinnervation, nerve transfer

INTRODUCTION

Chronic neurogenic pain is a common sequela of lower extremity injury and a complication that can be difficult to manage despite multimodal therapy. And with over one million lower extremity amputations performed globally annually, post-amputation pain represents a significant burden to both patients and providers[1]. Post-amputation pain, which has been reported in up to 95% of amputees, typically includes both residual limb pain as well as phantom limb pain[2,3]. Residual limb pain (RLP) is defined as pain localized to the remaining limb after amputation and is felt to be mediated by neuroma formation in a typical post-surgical pathway[3]. Phantom limb pain (PLP) is characterized by painful sensations in the lost body part and can be either nociceptive or neuropathic in nature[3,4]. While these two types of pain are distinct clinical entities, there does appear to be a significant correlation between residual limb pain and phantom limb pain[5].

Although both surgical and non-surgical treatment modalities have been trialed for post-amputation pain, the surgical procedure of targeted muscle reinnervation (TMR) has gained traction as an effective and reproducible tool in relieving both types of post-amputation pain[6-8]. TMR was originally conceptualized as a technique to power myoelectric upper extremity prostheses and serendipitously found to be effective in relieving amputee pain[1,9,10]. After early, promising data using this technique, a subsequent meta-analysis of retrospective data and randomized control trials have demonstrated significant reductions in phantom limb pain and residual limb when TMR is performed either in a primary or secondary fashion[1,8].

This study is a systematic review of primary data on patient-reported outcomes following primary and secondary TMR for the treatment of residual limb pain. We specifically focus on TMR of the lower extremities for treatment of residual limb pain, as lower extremity myoelectric prosthetic use is limited, unlike indications for upper extremity TMR.

METHODS

A literature search for all studies that met inclusion criteria were evaluated for the specific outcome tools used to assess improvement in pain following TMR. Studies using the same outcome tool were summarily aggregated to quantify the degree of improvement in lower extremity PLP and RLP following TMR. For this review, a meta-analysis was not applicable due to possible heterogeneity including mechanism of limb injury, time to treatment, length of follow-up, variability in nerve transfer techniques, and type of outcome measures. Therefore, descriptive statistics have been employed to represent the data to provide a general update on the use and effectiveness of this technique. The PRISMA checklist was followed throughout this study's design and execution[11].

Literature search

A literature review of English-language publications was performed from January 1997 to April 2022 using MEDLINE, EMBASE, and PubMed databases to identify publications related to targeted muscle reinnervation and limb pain. All three databases were queried using the same keywords: "targeted muscle reinnervation" AND "pain". Abstracts were reviewed in each of the database queries and duplicates were eliminated. Next, abstracts and titles were reviewed using the inclusion and exclusion criteria. Finally, one reviewer conducted a formal review of the remaining full-text articles, specifically looking for demographic information, clinical information, techniques used, and pain outcome tools.

Inclusion and exclusion criteria

Inclusion criteria are included in Table 1. In summary, we identified original English language articles studying targeted muscle reinnervation as a primary or secondary treatment for lower extremity PLP, RLP

Table 1. Inclusion criteria for review of the literature for targeted muscle reinnervation in the treatment of lower extremity limb pain

Literature type	Original article with primary data Human subjects English language publication
Treatment	Targeted muscle reinnervation Primary treatment Secondary treatment
Indication	*Lower extremity pain Phantom limb pain Residual limb pain General limb pain
Type of nerve injury	Amputation Iatrogenic injury
Report of pain outcome	Numerical rating system PROMIS Visual analog scale Incidence of limb pain

*Exceptions made for studies combining upper and lower extremities in analysis.

and general limb pain (GLP). After initial review, several studies that met our inclusion criteria had combined analysis of upper and lower extremity TMR and the lower extremity data pool was extracted for final analysis. Studies were categorized based on the timing of surgical intervention, either primary or secondary.

Articles were excluded if they reported on one of the following: (1) Focus on TMR for myoelectric prosthetic control; (2) upper extremity TMR only; (3) evaluation of outcomes in regenerative peripheral nerve interfaces for the treatment of limb pain; (4) single case reports; (5) systematic reviews, technique reviews, or anatomical studies; and (6) failure to include patient-reported outcome data. Upper extremity studies were excluded as our team was specifically interested in lower extremity outcomes, as TMR in the upper extremity is most often used for myoelectric prosthetic control. By excluding upper extremity TMR studies, we were able to isolate our study to those primarily studying pain as the indication for surgery and exclude studies that secondarily studied pain as a result of TMR for myoelectric prosthetic control.

Data extraction and statistical analysis

After a formal review of all relevant articles, one reviewer obtained data including patient demographics, clinical and procedural characteristics, and pain outcomes including Patient-Reported Outcome Measurement Information System (PROMIS) scores, numerical rating scale (NRS) scores, and incidence of limb pain. Pain outcomes data was aggregated when appropriate and summarized for analysis.

PROMIS scores for pain behavior, pain intensity and pain interference instruments were reported in the studies included in this review. PROMIS scores for each instrument can be reported in two ways - raw summary score or T-score. PROMIS raw scores are rescaled into standardized T-scores where a score of 50 is the mean of a relevant reference population and 10 is the standard deviation of that reference population[12]. T-scores facilitate comparisons between scales with different lengths and allow for standardization relevant to population norms. A higher T-score represents higher pain interference. Studies that reported PROMIS raw scores were converted to T-scores using corresponding scoring guides for the various instruments[13]. Changes in PROMIS scores, when reported, were also converted to changes in T-scores.

Statistical analyses of quantifiable measures of pain were summarized with weight averages considering the number of patients and the reported mean score (PROMIS, NRS, or VAS). Outcomes reported as medians were treated as means to simplify the aggregation across studies. Standard deviations for pain outcomes were not calculated given this assumption, as outcomes reported as medians lacked standard deviations. No adjustments were made for studies that combined upper and lower extremity outcomes in their results. When studies did report separate outcomes for upper and lower extremities, only lower extremity outcomes were included in our analysis. The analysis of indications for TMR was a summation of the number of extremities operated on rather than the number of patients. When possible, upper extremities were excluded from this analysis. Incidences of PLP, RLP and GLP were simply totaled. All statistical analyses were performed in Microsoft Excel version 16.6 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

Study retrieval and characteristics

This review started with 299 citations identified across three databases. A flow diagram is included in Figure 1, demonstrating the study's inclusion and exclusion criteria. After eliminating all duplicate citations across the databases and initial review of titles and abstracts, 16 citations were thoroughly reviewed.

The final tally included ten studies with primary data evaluating pain outcomes following TMR for a total of 414 patients. Only two studies (174 patients) evaluated outcomes in lower extremity TMR exclusively, with eight studies (240 patients) combining upper and lower extremity TMR outcomes. Nine of the studies were conducted in the United States and one in the United Kingdom. Two studies were prospective in nature, one of which was a randomized control trial, and eight were retrospective cohort studies. Four studies exclusively reported outcomes in secondary TMR for the treatment of pain, four other studies reported outcomes in primary TMR, and two studies reported outcomes in both primary and secondary TMR.

Although 80% of the studies retrieved combined upper and lower extremity TMR outcomes, we isolated outcomes for lower extremity TMR whenever possible. A total of 431 limbs were included in this review, 341 (79.1%) were lower extremity TMR and 90 (20.9%) were upper extremity TMR. Of note, one study specifically evaluated TMR in the treatment of neuroma pain in nonamputees[14]. All other studies reported TMR outcomes in the setting of extremity amputation. A summary of all studies is included in Tables 2 and 3.

Indications

Among the 431 upper and lower extremity limbs in this review, we were able to categorize all lower extremities based on the mechanism of injury leading to primary or secondary TMR. Due to the constraints of several studies combining data between upper and lower extremities, 46 upper extremities were included in the aggregation. Therefore, a total of 387 limbs were included in Figure 2. 2.1% of all TMR was performed for nonamputees. The most common indication for amputation was trauma (44.7%), which included military and non-military ballistic injuries as well as motor vehicle collisions. Infection was the second most common indication for amputation (25.1%), followed by oncologic amputation (12.7%).

TMR for primary treatment of pain

A total of 206 lower extremity limbs in six studies were treated primarily with TMR to prevent lower extremity pain [Table 2]. Primary TMR was most performed during the time of amputation in the setting of lower extremity infection (42.5%). Oncologic amputation (19.8%) and lower extremity trauma (18.4%) were the next most common indications for primary TMR.

Table 2. Studies and patient demographics, targeted muscle reinnervation for primary treatment of limb pain

Study	Country	Total patients	Total lower extremities	Age (yr)	% Male	Follow-up (mo)	Primary pain outcome	TMR technique
Chang *et al.*, 2021[20]	United States	100	100	59	70%	9.6	Incidence of PLP, RLP, GLP after the last follow-up	SPN -> EDL TN -> deep posterior compartment
Hoyt *et al.*, 2021[18]	United States	74	28	35*	81%	14*	Numerical rating GLP	Sciatic -> gluteus maximus Proximal TN -> semimembranosus CPN -> biceps femoris Femoral -> quadricep Distal TN -> soleus or lat. Gastrocnemius SPN -> EDL or EHL Sural -> FHL or gastrocnemius
Valerio *et al.*, 2019[15]	United States	51	36	n/a**	59%	11.*	Median PROMIS raw scores for RLP, PLP NRS for RLP, PLP	Nonspecific TMR
Frantz *et al.*, 2020[16]	United States	25	20	47.5	60%	14.1	Median PROMIS raw scores for RLP, PLP	TN -> gastrocnemius, soleus, or tibialis posterior CPN -> tibialis anterior, peroneus longus/brevis, medial soleus SPN -> peroneus brevis/longus Saphenous -> medial gastrocnemius, medial soleus Sural -> lateral gastrocnemius, lateral soleus, tibialis posterior
Pet *et al.*, 2014[19]	United States	12	1	34.0	100%	22	Incidence of PLP, RLP, GLP after one year	TN -> gastrocnemius, soleus, or tibialis posterior CPN -> tibialis anterior, peroneus longus/brevis, medial soleus SPN -> peroneus brevis/longus Saphenous -> medial gastrocnemius, medial soleus Sural -> lateral gastrocnemius, lateral soleus, tibialis posterior
Alexander *et al.*, 2019[17]	United States	31	21	49.4	66%	14.7	Mean PROMIS raw scores for RLP, PLP	Nonspecific TMR

*Median reported; **neither median nor mean reported. Study reported a range of ages. GLP: General limb pain; PLP: phantom limb pain; RLP: residual limb pain; SPN: superficial peroneal nerve; EDL: extensor digitorum longus; TN: tibial nerve; CPN: common peroneal nerve; FHL: flexor hallucis longus.

Pain outcomes were variably reported, although all studies reported a decrease in limb pain. Median PROMIS T-scores were used in two studies to quantify pain intensity, behavior and interference for both PLP and RLP at 1-year follow-up (Valerio and Frantz). The average follow-up was 12.6 months between both Valerio *et al.*[15] and Frantz *et al.*[16]. Average PLP intensity, behavior, and interference scores were 36.3, 49.6, and 44.0, respectively, and were below the average T-score on the PROMIS scale (mean T-score = 50)[15,16]. Average RLP intensity, behavior, and interference scores were 32.5, 35.8 and 44.0, respectively, and, were below average T-score on the PROMIS scale [Table 4]. Valerio *et al.* and Alexander *et al.* compared PROMIS scores between primary TMR patients and control groups of amputees without TMR at 1-year follow-up[15,17]. PLP and RLP scores for intensity, behavior and interference were less in the TMR group in all categories and demonstrated an average difference of > 10 in four categories - PLP interference, RLP intensity, behavior and interference - which equates to a difference of 1 standard deviation on the PROMIS scale [Table 5].

Table 3. Studies and patient demographics, targeted muscle reinnervation for secondary treatment of limb pain

Study	Country	Total patients	Total lower extremities	Age (yr)	% Male	Follow-up (mo)	Primary pain outcome	TMR technique
Dumanian *et al.*, 2019[21]	United States	14	12	39.6	86%	17.7	Change in mean PROMIS T scores for RLP, PLP Change in mean NRS scores for worst RLP, PLP	Nonspecific TMR
Mioton *et al.*, 2020[7]	United States	33	14	42.2	85%	12	Change in mean PROMIS T-scores for RLP, PLP Change in mean NRS scores for worst RLP, PLP	Nonspecific TMR
Kang *et al.*, 2021[22]	United Kingdom	36	29	49	75%	19.9	Change in mean NRS scores for worst RLP, PLP	Sciatic -> biceps femoris, semimembranosus, or semitendinosus CPN -> lateral gastrocnemius TN -> soleus or medial gastrocnemius
Hoyt *et al.*, 2021[18]	United States	74	59	35*	81%	14*	Change in numerical pain rating for GLP	Sciatic -> gluteus maximus Proximal TN -> semimembranosus CPN -> biceps femoris Femoral -> quadricep Distal TN -> soleus or lat. Gastrocnemius SPN -> EDL or EHL Sural -> FHL or gastrocnemius
Chang *et al.*, 2020[14]	United States	15	9	53.1	n/a**	22.0	Change in numerical pain rating for GLP	SPN -> EDL, peroneus brevis, or tibialis anterior DPN -> EHL Sural -> medial gastrocnemius or peroneus brevis Saphenous -> medial gastrocnemius
Pet *et al.*, 2014[19]	United States	23	15	44	52%	8.1	Incidence of RLP, PLP before and after TMR	TN -> semimembranosus or semitendinosus CPN -> biceps femoris

*Median reported. **not reported. GLP: General limb pain; PLP: phantom limb pain; RLP: residual limb pain; SPN: superficial peroneal nerve; EDL: extensor digitorum longus; TN: tibial nerve; CPN: common peroneal nerve; FHL: flexor hallucis longus; EHL: extensor hallucis longus; DPN: deep peroneal nerve.

Table 4. Average PROMIS T-Scores for phantom and residual limb pain at the last follow-up after primary targeted muscle reinnervation

			PROMIS T-scores for PLP			PROMIS T-scores for RLP		
Study	Follow-up (mo)	Patients	Intensity	Behavior	Interference	Intensity	Behavior	Interference
Valerio *et al.*[15]±	11	51	36.3	50.1	40.7	30.7	36.7	40.7
Frantz *et al.*[16]*	14.1	25	36.3	48.6	50.7	36.3	34.1	50.7
Average			36.3	49.6	44.0	32.5	35.8	44.0

±Valerio *et al.* reported median PROMIS T-scores; scores include 15 UE's. *Frantz *et al.* reported median PROMIS raw scores, converted to T-scores using conversion tables; scores include 5 UE's.

Hoyt *et al.*[18] and Valerio *et al.*[15] reported general pain scores and numerical rating scales for PLP and RLP, respectively. Hoyt demonstrated a decrease of 3.2 points in general limb pain when comparing TMR patients from baseline to final follow-up[18]. Valerio reported an average difference in PLP and RLP NRS

Table 5. Average difference in PROMIS T-Scores for phantom and residual limb pain between TMR and non-TMR patients after primary TMR

			Difference in PROMIS T-scores for PLP			Difference in PROMIS T-scores for RLP		
Study	**Follow-up (mo)**	**Patients**	**Intensity**	**Behavior**	**Interference**	**Intensity**	**Behavior**	**Interference**
Valerio *et al.*[15]±	11	51	-12.1	-6.5	-15.1	-16.1	-20.6	-16.6
Alexander *et al.*[17]*	14.7	31	-5.85	-5.9	-7.44	-5.48	-6.2	-6.82
Average			-9.7	-6.3	-12.2	-12.1	-15.2	-12.9

±Valerio *et al.* differed in PROMIS scores in comparison to the study's control group; scores include 15 UE's. *Alexander *et al.* differed in PROMIS scores in comparison to the study's control group; scores include 10 UE's.

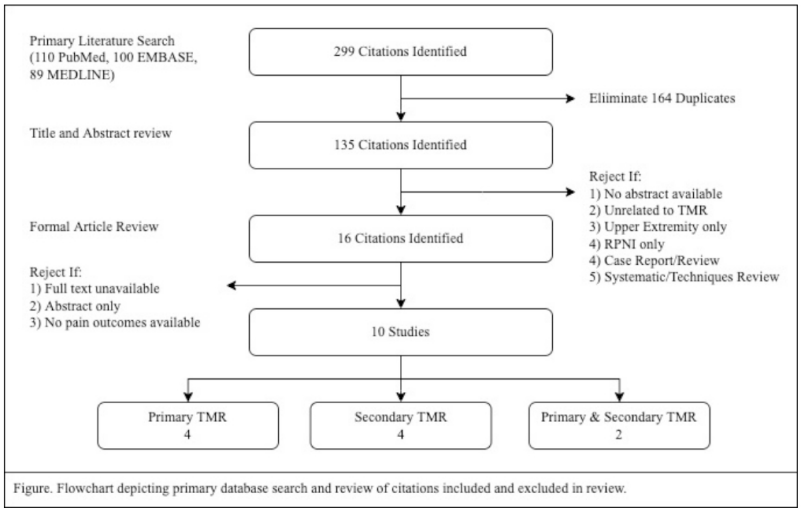

Figure 1. Flowchart of database search and references retrieved and excluded from review.

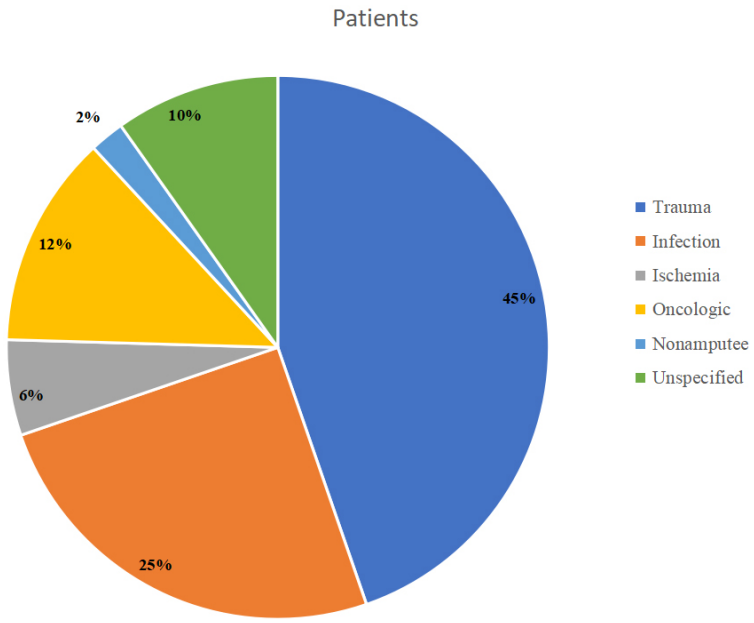

Figure 2. Pie chart of indications for amputation and targeted muscle reinnervation, primary or secondary treatment of pain.

scores of -4.0 and -3.0, respectively, compared to the non-TMR group[15].

The remaining two studies reported the incidence of PLP and RLP. Pet *et al.* reported one primary TMR in the lower extremity and the patient reported no PLP or RLP at 1-year follow-up[19]. Chang *et al.* compared 100 primary TMRs in below-knee amputees to 100 non-TMR amputees and, at 1-year follow-up, reported a significant difference in PLP (19% in TMR *vs.* 47% in non-TMR) and RLP incidence rates (14% *vs.* 57%)[20] .

It is important to note that three studies (Valerio, Frantz, and Alexander) reported results that did not distinguish between upper extremity and lower extremity patients. PROMIS T-scores did not solely reflect lower extremity pain, although, between these three studies, only 28.0% (30/107 limbs) of the TMR limbs in these studies were upper extremities[15-17].

TMR for secondary treatment of pain

A total of 138 lower limbs were treated secondarily with TMR in the setting of residual, phantom, and or general limb pain, often following amputation [Table 3]. Secondary TMR for lower extremity residual limb pain, phantom limb pain, and general limb pain was most performed after amputation in the setting of prior lower extremity trauma (73.4%). Amputation for infection was the next most common indication for secondary TMR (7.4%). Another 7.4% of nonamputee patients had TMR in the setting of post-operative neuroma pain.

Five studies reported pain scores with NRS. Mioton *et al*, Dumanian *et al*, and Kang *et al.* comprised 67 patients and reported a mean decrease in PLP and RLP NRS scores of 2.63 and 3.23, respectively, from 1-year follow-up to baseline pain scores[7,21,22]. Hoyt *et al.* and Chang *et al.* totaled 89 patients and presented a mean decrease in general pain score of 2.8 points from the last follow-up to baseline[14,18] [Table 6].

Two studies for a total of 47 patients reported mean changes in PROMIS T-scores between baseline and 1-year follow-up. The average decrease in PLP intensity, behavior and interference T-scores were 8.36, 5.70 and 7.76, respectively. The average decrease in RLP intensity, behavior and interference T-scores were 9.74, 4.21 and 8.37, respectively[7,21] [Table 7].

In the remaining study, Pet *et al*, reported incidence of PLP and RLP before TMR and at the last follow-up (mean = 22 months). Incidence of PLP decreased from 26.7% (4/15 patients) to 20% (3/15 patients). Incidence of RLP decreased from 100% (15/15) to 6.67% (1/15)[19].

The studies reporting NRS, VAS, and/or PROMIS scores included some upper extremity TMR patients. Of the five studies, 19.9% (39/196 limbs) of the TMR limbs were upper extremities[7,14,21,22]. The summarized results of Pet *et al.* excluded all upper extremity TMR patients[19].

DISCUSSION

The incidence of chronic pain following amputation of the lower extremity is nearly universal[2]. In and of itself, this simple conclusion is rather remarkable and stands in stark contrast to the rapid advancements made in limb salvage and restoration over the past 50 years. As awareness of this deficit in our care of amputees has grown, novel solutions including TMR, RPNI, and relocation nerve grafting have emerged. As TMR techniques have developed and become more widely adopted, the body of research has matured from observational to level 1 evidence. This study aims to assess all available evidence in support of TMR for the treatment of PLP and RLP for which pain outcomes are available. Notably, all studies queried reported improvement in pain following TMR for the lower extremity.

Table 6. Average change in the numerical rating of phantom, residual and general limb pain after secondary targeted muscle reinnervation comparing baseline to follow-up pain

Study	Follow-up (mo)	Patients	Mean change in NRS PLP	Mean change in NRS RLP	Mean change in NRS GLP
Dumanian *et al.*[21]α	17.7	14	-3.2	-2.9	
Mioton *et al.*[7]β	12	33	-2.4	-2.7	
Kang *et al.*[22]ψ	19.9	20	-2.6	-4.4	
Hoyt *et al.*[18]*	14	74			-2.6
Chang *et al.*[14]τ	8.1	15			-3.6
Average			-2.6	-3.2	-2.8

αDumanian *et al.* reported changes at 1-year follow-up; included 3 UE's. βMioton *et al.* reported changes at 1-year follow-up; includes 19 UE's. ψKang *et al.* reported changes at 1-year follow-up; no UE patients were included. *Hoyt *et al.* reported changes at the last follow-up; no UE's in the study. τChang *et al.* reported changes at the last follow-up; included 5 UE's.

Table 7. Average change in PROMIS T-score of phantom, residual and general limb pain after secondary targeted muscle reinnervation comparing baseline to follow-up pain

			Change in PROMIS T-scores for PLP			Change in PROMIS T-scores for RLP		
Study	Follow-up (mo)	Patients	Intensity	Behavior	Interference	Intensity	Behavior	Interference
Dumanian *et al.*[21]±	17.7	14	-13.7	-7.6	-9.8	-11.5	-4.7	-7.6
Mioton *et al.*[7]*	12	33	-6.1	-4.9	-6.9	-9.0	-4.0	-8.7
Average			-8.4	-5.7	-7.8	-9.7	-4.2	-8.4

±Dumanian *et al.* reported changes in PROMIS T-scores from baseline to 1-year follow-up; included 3 UE's. *Mioton *et al.* reported changes in PROMIS T-scores from baseline to 1-year follow-up; included 19 UE's.

Among the limitations of the assessment of TMR as a modality for post-amputation pain is the heterogeneity of pain assessment tools. Tools such as the NRS, Verbal Rating Scales (VRS), Visual Analog Scales (VAS), and the Faces Pain Scale-Revised (FPS-R) are the most common rating scales available; however, these represent one-dimensional, single time point assessments of a complex, multifactorial problem[23,24]. More complex pain assessments like the PROMIS pain behavior, intensity, and interference instruments provide a measurement of well-being or suffering as a result of pain[25,26]. Further, adjuncts or proxy measurements like the Amputee Mobility Predictor (AMP), Prosthetic Evaluation Questionnaire (PEQ), Patient-Specific Functional Scale (PSFS), *etc*. have been utilized to assess outcomes of amputations and quality of life[27].

PROMIS was created by the National Institutes of Health (NIH) as a tool for the measurement of physical, mental and social health of patients with chronic conditions. Several validated PROMIS surveys were used by the authors, including PROMIS-Pain Intensity, which includes the typical 0-10 pain numerical rating scale, PROMIS-Pain Interference, assessing the degree to which the pain inhibits activities of daily life and mental well-being, and the PROMIS-Behavior, evaluating the effect on pain as it relates to patient movement, affect, and social interactions. These scores can be transformed to T-score distributions with a mean of 50 and a standard deviation of 10, with a lower score reflective of decreased pain. Most PROMIS pain T-scores in the primary TMR studies were found to have a profound decrease of at least one standard deviation when comparing T-scores to the respective study's control groups[15,17]. Only PROMIS-Behavior for PLP (T-score-6.3) and PROMIS - Intensity for PLP (T-score-9.7) were below the one standard deviation change. Preventive treatment seems to be very beneficial, although there is reporting bias in this comparison as the control patients are surveyed anonymously and neither study is randomized[15,17]. It would be valuable to perform a prospective randomized study comparing pain outcomes in amputees undergoing primary TMR against those who do not. When comparing PROMIS scores to the relevant reference population

(mean = 50, SD = 10), Valerio and Frantz *et al.* demonstrated pain scores lower than the average patient in all PROMIS pain categories for PLP and RLP at final follow-up[15,16]. Thus, if there is reporting bias in the reporting of pain scores by the control groups in Valerio and Alexander *et al*, we can still comfortably assume primary TMR does help control limb pain after amputation[17].

Improvements in PROMIS T-scores for secondary TMR were more modest, with all score changes within one standard deviation. In fact, in all PROMIS categories for RLP and PLP, the magnitude of benefit derived after primary TMR was greater than that derived after secondary TMR. There are several possible explanations for this finding, including pain chronification. Pain chronification has been explored and is a process that theorizes a mechanism that connects chronic pain to memory. Longitudinal neuroimaging has demonstrated that brain anatomy pertaining to memory, the hippocampus and amygdala changes in patients with chronic pain. This reorganization could explain why secondary TMR benefits for pain could be blunted in comparison to primary TMR[28]. The data from Dumanian *et al.* and Mioton *et al.* both suggest that PLP and RLP can still benefit from secondary TMR, even years after amputation, especially compared to conventional neuroma excision and nerve end burying into muscle techniques[7,21]. The median time to TMR after amputation in Dumanian *et al.* was 5-9 years and 1-4 years in Mioton *et al.*[7,21].

Pain interference scores had consistently great improvements across RLP and PLP in primary and secondary TMR. In primary TMR, RLP and PLP pain interference scores decreased by more than one standard deviation, and in secondary TMR, those scores approached one standard deviation of change. Pain interference reflects the patient's engagement with social, cognitive, emotional, physical, and recreational activities. TMR not only can reduce limb pain severity but also enable patients to engage with society with a sense of normalcy, which many patients would argue is more important than intensity improvements alone. Intensity scores, though, also saw consistent improvements across RLP and PLP after primary and secondary TMR. This improvement was also supported by NRS scores in secondary TMR. Surgeons can advise patients with this data that pain and quality of life have the potential for improvement following TMR.

The pain numeric rating scale (NRS), on which patients rate their current pain intensity from 0 ("no pain") to 10 ("worst possible pain"), has become the most widely used instrument for pain screening. A reduction of 2 points, or 30%, represents a clinically important difference in pain[29]. By this measure, clinically significant improvements in both PLP and RLP were seen, of 2.6 and 3.2, respectively, as well as improvements in general limb pain as documented by two authors, with a reduction of 2.8[7,14,18,21,22]. Although not as precise as the PROMIS questionnaires or reflective of the quality of life effects, NRS scores provide a quantifiable change in pain. Studies should prioritize quantifiable measures of limb pain rather than the presence or absence of limb pain, as there is almost always a spectrum of the degree and experience of pain.

There are several limitations of this study. First, selection bias is introduced in multiple studies evaluating primary TMR as control patients were assessed by outreach through conferences and not withholding TMR from eligible patients, or by comparison to historical, published outcomes treatments[15,17]. Second, the data includes TMR performed for all reasons, including trauma, infection and oncological. This introduces aggregation bias wherein these populations may be inappropriately combined. Third, technical execution differs between and even within study groups. This reflects the inherent nature of TMR, wherein the pattern of nerve transfers may vary from patient to patient, depending on the anatomy and amputation level. Moreover, management of size mismatch in nerve coaptation may vary from group to group, with the continued evolution of techniques[30].

This review demonstrated that there is a growing body of evidence supporting TMR for primary and secondary treatment of amputee pain, residual limb pain, phantom limb pain and general limb pain. Patients, on average, experience improvements in pain intensity after primary and secondary TMR. PROMIS instruments offer providers and patients the opportunity to precisely quantify the level of pain intensity, behavioral changes and social effects of post-amputation limb pain, as well as the potential for improvement with TMR.

Future studies evaluating the impact of primary TMR should aim to eliminate selection bias by carefully selecting control patients. Additionally, future studies should assess not only measures of pain, but also patient-centric outcomes such as the ability to wear a prosthetic (Orthotics and Prosthetics Users Survey, return to work, and decreased need for adjunctive medical therapies including opioid use).

Additionally, while commonly used in research, PROMIS scores should be converted to plain language descriptions to help patients and providers communicate effectively and understand the clinical impact of the findings.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis, data acquisition and interpretation, as well as provided administrative, technical, and material support: Le ELH, Greyson MA, Constantine RS, Iorio ML

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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